Effects of soft tissue augmentation procedures on peri-implant health or disease: A systematic review and meta-analysis

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Abstract: OBJECTIVE To review the dental literature in terms of soft tissue augmentation procedures and their influence on peri-implant health or disease in partially and fully edentulous patients. METHODS A MEDLINE search from 1966 to 2016 was performed to identify controlled clinical studies comparing soft tissue grafting versus no soft tissue grafting (maintenance) or two types of soft tissue grafting procedures at implant sites. The soft tissue grafting procedures included either an increase of keratinized tissue or an increase of the thickness of the peri-implant mucosa. Studies reporting on the peri-implant tissue health, as assessed by bleeding or gingival indices, were included in the review. The search was complemented by an additional hand search of all selected full-text articles and reviews published between 2011 and 2016. The initial search yielded a total number of 2,823 studies. Eligible studies were selected based on the inclusion criteria (finally included: four studies on gain of keratinized tissue; six studies on gain of mucosal thickness) and quality assessments conducted. Meta-analyses were applied whenever possible. RESULTS Soft tissue grafting procedures for gain of keratinized tissue resulted in a significantly greater improvement of gingival index values compared to maintenance groups (with or without keratinized tissue) [n = 2; WMD = 0.863; 95% CI (0.658; 1.067); p < .001]. For final marginal bone levels, statistically significant differences were calculated in favor of an apically positioned flap (APF) plus autogenous grafts versus all control treatments (APF alone; APF plus a collagen matrix; maintenance without intervention [with or without residual keratinized tissue]) [n = 4; WMD = -0.175 mm; 95% CI: (-0.313; -0.037); p = .013]. Soft tissue grafting procedures for gain of mucosal thickness did not result in significant improvements in bleeding indices over time, but in significantly less marginal bone loss over time [WMD = 0.110; 95% CI: 0.067; 0.154; p < .001] and a borderline significance for marginal bone levels at the study endpoints compared to sites without grafting. CONCLUSIONS Within the limitations of this review, it was concluded that soft tissue grafting procedures result in more favorable peri-implant health: (i) for gain of keratinized mucosa using autogenous grafts with a greater improvement of bleeding indices and higher marginal bone levels; (ii) for gain of mucosal thickness using autogenous grafts with significantly less marginal bone loss.

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REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Effects of soft tissue augmentation procedures on peri-implant health or disease: A systematic review and meta-analysis

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Abstract

Objective: To review the dental literature in terms of soft tissue augmentation procedures and their influence on peri-implant health or disease in partially and fully edentulous patients.

Methods: A MEDLINE search from 1966 to 2016 was performed to identify controlled clinical studies comparing soft tissue grafting versus no soft tissue grafting (maintenance) or two types of soft tissue grafting procedures at implant sites. The soft tissue grafting procedures included either an increase of keratinized tissue or an increase of the thickness of the peri-implant mucosa. Studies reporting on the peri-implant tissue health, as assessed by bleeding or gingival indices, were included in the review. The search was complemented by an additional hand search of all selected full-text articles and reviews published between 2011 and 2016. The initial search yielded a total number of 2,823 studies. Eligible studies were selected based on the inclusion criteria (finally included: four studies on gain of keratinized tissue; six studies on gain of mucosal thickness) and quality assessments conducted. Meta-analyses were applied whenever possible.

Results: Soft tissue grafting procedures for gain of keratinized tissue resulted in a significantly greater improvement of gingival index values compared to maintenance groups (with or without keratinized tissue) [n = 2; WMD = 0.863; 95% CI (0.658; 1.067); p < .001]. For final marginal bone levels, statistically significant differences were calculated in favor of an apically positioned flap (APF) plus autogenous grafts versus all control treatments (APF alone; APF plus a collagen matrix; maintenance without intervention [with or without residual keratinized tissue]) [n = 4; WMD = −0.175 mm; 95% CI: (−0.313; −0.037); p = .013]. Soft tissue grafting procedures for gain of mucosal thickness did not result in significant improvements in bleeding indices over time, but in significantly less marginal bone loss over time [WMD = 0.110; 95% CI: 0.067; 0.154; p < .001] and a borderline significance for marginal bone levels at the study endpoints compared to sites without grafting.

Conclusions: Within the limitations of this review, it was concluded that soft tissue grafting procedures result in more favorable peri-implant health: (i) for gain of keratinized mucosa using autogenous grafts with a greater improvement of bleeding indices

and higher marginal bone levels; (ii) for gain of mucosal thickness using autogenous grafts with significantly less marginal bone loss.

KEYWORDS
bleeding on probing, complication, dental implant, free gingival graft, gingival index, peri-implant mucositis, peri-implantitis, periodontal probing depth, soft tissue, subepithelial connective tissue graft, systematic review

1 | INTRODUCTION

Soft tissue grafting procedures are increasingly performed for a number of indications in conjunction with dental implant therapy (Thoma, Buranawat, Hammerle, Held & Jung, 2014). Major clinical indications include recession coverage, gain of keratinized tissue (KT), and augmentation of soft tissue volume (STV; Basegmez, Ersanli, Demirel, Bolukbasi & Yalcin, 2012; Lorenzo, Garcia, Orsini, Martin & Sanz, 2012; Roccuzzo, Gaudioso, Bunino & Dalmasso, 2014; Thoma, Zeltner, et al., 2016). These periodontal plastic surgical procedures have been recommended to establish short- and long-term favorable biological, functional, and aesthetic outcomes. From a biological point of view, scientific evidence reports controversial data for the width of KT (Lin, Chan & Wang, 2013; Wennstrom & Derks, 2012). A lack of KT was not considered to be crucial in maintaining the health of peri-implant soft tissues (Wennstrom, Bengazi & Lekholm, 1994), to be associated with more bone loss (Chung, Oh, Shotwell, Misch & Wang, 2006), or to be more prone to peri-implant disease (Roos-Jansaker, Renvert, Lindahl & Renvert, 2006). Further studies reported, however, that a wider zone of KT may better preserve soft and hard tissue stability (Bouri, Bissada, Al-Zahrani, Faddoul & Nouneh, 2008), may be more favorable for the long-term maintenance of dental implants (Kim et al., 2009) and may result in better oral hygiene and less recession over time (Schrott, Jimenez, Hwang, Fiorellini & Weber, 2009). From an aesthetic point of view, a number of in vitro and clinical studies demonstrated a critical threshold value of 2-mm mucosal thickness for implant-borne reconstruction and reconstructive materials less discoloration of the soft tissues (Ioannidis et al., 2017; Jung, Sailer, Hammerle, Attin & Schmidlin, 2007; Jung et al., 2008; Thoma, Brandenberg, et al., 2016), as well as superior aesthetic outcomes compared to implant sites without grafting (Cornelini, Barone & Covani, 2008; Kan, Rungcharassaeng, Morimoto & Lozada, 2009). Moreover, an increased soft tissue thickness (thick biotype) may decrease the risk of recessions with immediate implants (Evans & Chen, 2008). Surgical procedures to augment soft tissue volume were therefore recommended in the esthetic zone mainly from an aesthetic point of view and to compensate for volume loss following tooth extraction and implant therapy with immediate or delayed placement protocols (Cosyn, De Bruyn & Cleymaet, 2013; Schneider, Grunder, Ender, Hammerle & Jung, 2011; Thoma, Zeltner, et al., 2016). From a biological point of view, no threshold value for a specific soft tissue thickness could be defined according to a recent systematic review (Akcali et al., 2016). Still, the major goal of implant therapy is to obtain long-term peri-implant health based on stable peri-implant soft tissue dimensions, low bleeding indices, and stable marginal bone levels. In summary, there is a lack of scientific recommendations whether or not to perform surgical procedures for gain of KT and for gain of mucosal thickness to establish peri-implant health and to limit the incidence of peri-implant disease. Neither do clinical suggestions exist for a specific soft tissue transplant to obtain more favorable outcomes. This question can only be answered by (randomized) controlled clinical trials comparing implant sites with and without soft tissue grafting and/or studies comparing different soft tissue transplants and techniques and reported outcome measures assessing peri-implant health.

The objective of this systematic review was to assess the effect of soft tissue grafting procedures to increase either the width of keratinized tissue or the mucosal thickness at dental implant sites in comparison with implant sites without soft tissue grafting procedures or with different grafting materials/transplants in terms of peri-implant health.

2 | MATERIAL AND METHODS

2.1 | Protocol development and eligibility criteria

A detailed protocol was developed and followed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Liberati et al., 2009; Moher et al., 2009).

2.2 | PICO questions

Population: systemically healthy patients with dental implants.

Intervention: soft tissue grafting procedures to increase the keratinized tissue or the mucosal thickness at dental implant sites.

Comparison: implant sites without soft tissue grafting procedures or with (a) different grafting materials/transplants.

Outcome:

- Primary outcome: peri-implant health measured by a bleeding index or gingival index.
- Secondary outcomes: probing depth values, marginal bone level changes, plaque index, time-point of intervention, type of material.

2.3 | Focused questions

In systemically healthy patients with dental implants, what is the effect of soft tissue grafting procedures to increase the width of keratinized

tissue or the mucosal thickness at dental implant sites in comparison with implant sites without soft tissue grafting procedures or with different grafting materials/transplants in terms of peri-implant health?

2.4 | Search strategy

An electronic MEDLINE (PubMed) search was performed for controlled clinical studies, including articles published from January 1, 1966 up to July 31, 2016 in the Dental literature. The search was limited to the English, German, and Spanish languages. Additionally, full-text articles of narrative and systematic reviews on similar topics published between January 2011 and July 2016 were obtained. An additional hand search was performed identifying relevant studies by screening these reviews and the reference list of all obtained full-text articles.

2.5 | Search terms

The following search terms were applied as follows:

("acellular dermal matrix" OR "dermal matrix allograft" OR "alloderm" OR "keratinized gingiva" OR "keratinized tissue" OR "soft tissue graft" OR "subepithelial connective tissue graft" OR "connective tissue"(MeSH term) OR "free gingival graft" OR "human fibroblast-derived dermal substitute" OR "dermagraft" OR "apligraf" OR "collagen matrix" OR "extracellular membrane" OR "gingival autograft" OR "attached gingiva" OR "attached mucosa" OR "keratinized mucosa" OR "soft tissue augmentation" OR "soft tissue transplantation" OR "vestibuloplasty" (MeSH term) OR "ridge augmentation" OR "soft tissue correction" OR "apically positioned flap")

AND

("dental implants" (MeSH term) OR "jaw, edentulous, partially" (MeSH term) OR "pontic" (MeSH term) OR "implant sites" OR "bleeding on probing" OR "sulcus bleeding index")

2.6 | Inclusion criteria

Clinical publications were considered if all of the following criteria were suitable: (i) human trials with a minimum amount of 10 patients (five per group), (ii) any controlled clinical study (CCT), (iii) follow-up of at least 3 months, (iv) reported outcome measures following the surgical intervention for gain of keratinized tissue or gain of mucosal thickness around dental implants including any peri-implant bleeding index/parameter, and (v) patients needed to have been examined clinically.

2.7 | Exclusion criteria

In vitro and preclinical studies, case series, case reports, and reports based on questionnaires, interviews and charts were excluded from the review as well as all studies not meeting the inclusion criteria. Moreover, studies dealing with treatment of recession defects and increase of keratinized tissue around teeth and soft tissue volume at pontic sites were not considered.

2.8 | Selection of studies

Two authors (DT, NN) independently screened the titles derived from the online search based on the inclusion criteria. Disagreements were solved by discussion. Subsequently, the abstracts of the selected titles were obtained and screened for meeting the inclusion criteria. If no abstract was available, the abstract of the printed article was used. Thereafter, full-text articles of the selected abstracts were obtained. If title and abstract did not provide sufficient information regarding the inclusion criteria, the full text was obtained as well. Again, disagreements were resolved by discussion, and Cohen's Kappa-coefficient was calculated as a measure of agreement between the two readers.

The final selection based on inclusion/exclusion criteria was made for the full-text articles. For this purpose, Material and Methods, Results, and Discussion of these studies were screened by two reviewers (DT, NN) and double-checked. Any questions that came up during the screening were discussed between the authors to aim for consensus. In case potential publications did not report (in detail) on peri-implant bleeding indices/parameters, authors were contacted and asked if they could provide additional data.

2.9 | Data extraction and method of analysis

All data were extracted independently by two reviewers (DTH, NN) using data extraction tables. Any disagreements were thereafter discussed to aim for consensus.

Information on the following parameters was extracted as follows: author(s), year of publication, study setting, study design, number of patients, age range, mean age, gender, dropouts, mean follow-up and range, periodontal status, smoking habits, systemic condition, type of intervention (test and control(s)), implant system, number of implants, number of implant failures, implant survival rate, probing depth (PD), bleeding on probing (BOP) or any other bleeding index, plaque index (PII) or any other gingival index, mid-facial mucosal level (MML), width of keratinized tissue (KT), mucosal thickness (MT), and marginal bone levels (MBL).

The primary outcome included BOP or any other bleeding/gingival index at the follow-up time-point(s). Secondary outcomes were PD, PII, MML, KT, MT, and MBL (changes).

2.10 | Quality assessment

Two reviewers (DT, NN) independently evaluated the methodological quality of all included studies using the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled clinical studies including six domains/questions (Higgins et al., 2011). The same tool was applied for controlled clinical trials, hereby omitting questions 2, 3, and 4. Again, disagreements were discussed to aim for consensus.

2.11 | Statistical analysis

To summarize and compare studies, mean and standard deviation (SD) values (change final baseline and final data) were directly pooled and

analyzed with weighted mean differences (WMDs) and 95% confidence intervals (CIs). In case of studies with more than two arms, each intervention was compared against the control group. Study-specific estimates were pooled with both the fixed- and random-effect models (DerSimonian & Laird, 1986), and the random-effect model results were presented.

Two groups of meta-analyses were performed based on the type of intervention:

- Interventions directed to increase the width of keratinized tissue (KT). The data for the control group were obtained from implants with xenogeneic soft tissue grafting or from implants with maintenance alone (no soft tissue grafting), whereas the test group comprised of the data from groups with autogenous soft tissue grafting procedures. In addition, a subgroup analysis was carried out on the selected outcome variables using the type of control procedures [apically position flap/vestibuloplasty (APF), maintenance (alveolar mucosa, keratinized mucosa [>0 mm, >2 mm, <2 mm]), apically positioned flap, and collagen matrix (XCM)] as explanatory variable.
- Interventions directed to augment the mucosal thickness (MT). In that case, the data for the control group were obtained from implants without soft tissue grafting, whereas the test group comprised of the data from groups with grafting procedures.

The statistical heterogeneity among studies was assessed using the *Q* test according to Dersimonian and Laird as well as the I2 index (Higgins et al., 2003), thus reporting the percentage of variation in the global estimate that was attributable to heterogeneity (I2 = 25%: low; I2 = 50%: moderate; I2 = 75%: high heterogeneity).

The publication bias was evaluated using Begg's and Egger's tests for small-study effects for gingival index change (in case of KT) and for BOP change (in case of MT). A sensitivity analysis of the meta-analysis results was also performed.

A forest plot was created to illustrate the effects in the meta-analysis of the different studies and the global estimation. STATA® (StataCorp LP, Lakeway Drive, College Station, Texas, USA) intercooled software was used to perform all analyses. Statistical significance was defined as a p value <.05.

3 | RESULTS

3.1 | Study characteristics

The electronic search identified a total of 2,823 titles (for details refer to Figure 1). From assessing the titles, 2,579 were excluded after discussion (inter-reader agreement $k = 0.75 \pm 0.31$). The resulting number of abstracts obtained was 244. Of these, 194 were excluded (inter-reader agreement $k = 0.67 \pm 0.31$). Subsequently, 50 full-text articles were obtained including 20 review articles. The additional hand search provided three more studies for gain of mucosal thickness (Bienz et al., 2017; Cosyn et al., 2016; Migliorati, Amorfini, Signori, Biavati & Benedicenti, 2015). Finally, 10 articles met the inclusion criteria, four articles for gain of keratinized tissue and six publications for gain of mucosal thickness (Table 1).

3.2 | Exclusion of studies

The authors of potentially excluded full texts were contacted to provide, if available, additional data. Reasons for excluding studies (n = 23, see reference list "List of excluded full-text articles and the reason for exclusion") after reading the full texts were as follows: insufficient data (e.g., no clinical parameters obtained/reported [BOP]; 17 studies), case reports (three), submerged implants (no data on implants) (one), no control group (one), and no soft tissue grafting performed (one) (see list of excluded studies).

3.3 | Quality assessment of the included studies

Table 2 summarizes the results of the quality assessment of the 10 included studies. Four of the included studies were RCTs (Basegmez, Karabuda, Demirel & Yalcin, 2013; Lorenzo et al., 2012; Migliorati et al., 2015; Yoshino, Kan, Rungcharassaeng, Roe & Lozada, 2014), and the full checklist (Cochrane Collaboration's tool for assessing the risk of bias) was applied, whereas for the remaining six studies (all CCTs), questions 2, 3, and 4 were omitted.

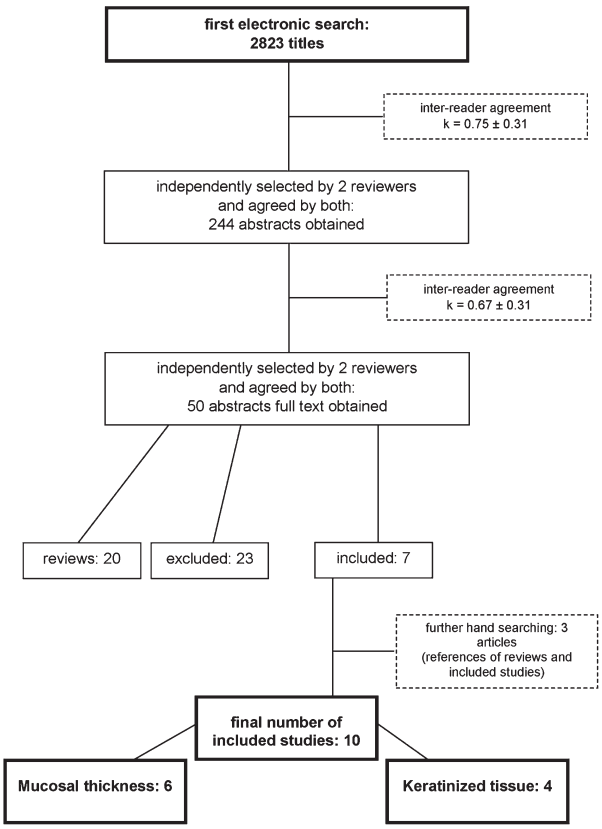

FIGURE 1 Search strategy. *For details and reasons for exclusion see Appendix S1 ("List of reviews" and "List of excluded full-text articles and the reason for exclusion")

3.3.1 | Keratinized tissue

The two included RCTs (Basegmez et al., 2012; Lorenzo et al., 2012) had a low risk of bias for all questions (random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessments, outcome data, reporting). The two CCTs were judged as having an unclear (Buyukozdemir Askin et al., 2015) or high (Roccuzzo, Grasso & Dalmasso, 2016) risk of selection (random sequence generation) bias. There was insufficient information regarding randomization allocation in one study (Buyukozdemir Askin et al., 2015), whereas in the other study, patients were allocated to a specific treatment according to the clinician's judgment (Roccuzzo et al., 2016). Concerning outcome and reporting bias, both CCTs were judged having a low risk.

For group imbalance and radiographic bias, the risks were considered to be low (Buyukozdemir Askin et al., 2015) or unclear (Roccuzzo et al., 2016). Clinician bias was either unclear (Buyukozdemir Askin et al., 2015) or low (Roccuzzo et al., 2016). Both did not perform a sample size calculation (Table 2).

Further factors that influenced bias were high patient numbers in both and a long follow-up period of 10 years in the latter study (Roccuzzo et al., 2016). All other included studies had follow-up periods between 6 and 12 months.

No publication bias was observed for GI change (main outcome variable) with the Egger test (p = .450) and with the Begg's test (.308).

3.3.2 | Mucosal thickness

The two included RCTs (Migliorati et al., 2015; Yoshino et al., 2014) were judged as having a low risk for selection bias since a block randomization generated by a statistician or a computer-generated random list was used. Concerning allocation concealment and blinding of researchers, both studies were considered to have an unclear risk since insufficient information was provided. One study was judged with a low risk, although the procedure did not allow the surgeon to be blinded for the treatment (Migliorati et al., 2015). Detection, attrition, and reporting bias were of low risk except for the blinding of the outcome assessment (Yoshino et al., 2014). Here, all data were gathered by a non-blinded single examiner (Yoshino et al., 2014), and thus, the detection bias was judged as unclear.

The random sequence allocation (selection bias) was judged as high risk in all four CCTs as they did either not explain the reason for the different treatment options (Bianchi & Sanfilippo, 2004) or the patients were divided into the groups upon the clinicians judgment (Bienz et al., 2017; Cosyn et al., 2016; Fenner, Hammerle, Sailer & Jung 2016). Attrition and outcome bias were considered to have a low risk of bias in all four studies. Further bias was judged with a low risk (Bianchi & Sanfilippo, 2004; Cosyn et al., 2016) and unclear risk due to a single examiner collecting the data (Fenner et al., 2016), no sample size calculation, and retrospective study design (Bienz et al., 2017; Fenner et al., 2016). (Table 2).

No publication bias for BOP changes was detected by Begg 's (p > .05) or Egger's tests (p = .767). The sensitivity analyses for this outcome showed that the exclusion of a single study did not substantially alter any estimate.

3.4 | Included studies

The 10 studies that met the inclusion criteria are presented in Table 1. Four studies were randomized controlled trials (RCTs) published between 2012 and 2014. Five studies were prospective, controlled clinical studies (CCTs), whereas one study was performed as a retrospective CCT (Bienz et al., 2017). All CCTs were published between 2004 and 2017. The studies were performed at University settings (n = 7) or in private practice (n = 2), whereas one study did not report on the setting. That particular study was designed as a two-center study (Lorenzo et al., 2012), whereas the remaining nine studies were single-center studies. The observation period and the reported data in all studies were at least 6 months.

TABLE 1 Study characteristics of the included studies

Author	Type of augmentation	Year	Type of study	Setting	Level of analysis
Lorenzo et al.	KT	2012	RCT	University and specialist (two center)	Patient
Basegmez et al.	KT	2012	RCT	University	Patient
Buyukozdemir Askin et al.	KT	2015	CCT	University	Implant
Roccuzzo et al.	KT	2016	CCT	Private practice	Patient
Bianchi and Sanfilippo	MT	2004	CCT	NR	Patient
Miglorati et al.	MT	2013	RCT	University	Patient
Yoshino et al.	MT	2014	RCT	University	Patient
Fenner et al.	MT	2016	CCT	University	Patient
Cosyn et al.	MT	2016	CCT	Private practice	Implant
Bienz et al.	MT	2017	CCT*	University	Patient

CCT, clinical controlled trial; CCT*, retrospective CCT; KT, keratinized tissue; MT, mucosal thickness; RCT, randomized controlled trial; NR, not reported.

TABLE 2 Risk-of-bias assessment of the included studies according to the "Cochrane Collaboration's Tool for assessing risk of bias." (a) Keratinized tissue; (b) Mucosal Thickness

(a)		Lorenzo et al. (2012) RCT	Basegmez et al. (2013) RCT	Buyukozdemir Askin et al. (2015)	Roccuzzo et al. (2016)
Random sequence generation (selection bias)	1)	Low risk	Low risk	Unclear risk	High risk
	2)	Code derived from a randomized list	Computer-generated random list	Insufficient information	According to clinician's judgment
Allocation concealment (selection bias)	1)	Low risk	Low risk	N/A	N/A
	2)	The randomization was performed at the day of surgery following the raising of a mucosal partial thickness flap/immediately before the application of the graft using a sealed envelope.	A sealed envelope was opened at the beginning of the surgical procedure following local anesthesia.	N/A	N/A
Blinding of participants and researchers (performance bias)	1)	Low risk	Low risk	N/A	N/A
	2)	The procedure did not allow the two surgeons to be blinded for the treatment. (autogenous vs substitute)	The procedure did not allow the two surgeons to be blinded for the treatment. (FGG vs vestibuloplasty)	N/A	N/A
Blinding of outcome assessments (detection bias)	1)	Low risk	Low risk	N/A	N/A
	2)	Blinded examiner different from the surgeon.	Trained examiner not involved in the surgeries.	N/A	N/A
Incomplete outcome data (attrition bias)	1)	Low risk	Low risk	Low risk	Low risk
	2)	Losses to follow-up were disclosed (two patients from the test group did not adhere to study protocol, i.e., smoking; one patient excluded from pain analysis due to trauma)	All gathered data reported/no dropouts	All gathered data reported/no dropouts	All gathered data reported/Losses to follow-up were disclosed (eight died; five moved; two had severe health problems; 16 refused final visit)
Selective reporting (reporting bias)	1)	Low risk	Low risk	Low risk	Low risk
	2)	All prespecified outcomes were reported.	All prespecified outcomes were reported.	All prespecified outcomes were reported.	All prespecified outcomes were reported.
Group imbalance	1)	Low risk	Low risk	Low risk	Unclear risk
	2)	Well-balanced groups with regard to: patient characteristics, location of selected sites, and clinical parameters at baseline.	Implants of the same type, at least 1 y in function had to present with: <1.5 mm attached mucosa and marginal movability w/o recession with signs of mucositis, but no bone loss	60 implants->3 groups: ≤2 mm (n = 20) received FGG ≤2 mm (n = 20) received maintenance >2 mm (n = 20) received maintenance	63 implants placed in KT 35 implants placed in AM -> 11 of these AM-patients received a FGG (up to the patient's choice)

(Continues)

TABLE 2 (Continued)

(a)		Lorenzo et al. (2012) RCT	Basegmez et al. (2013) RCT	Buyukozdemir Askin et al. (2015)	Roccuzzo et al. (2016)
Sample size	1)	Low risk	Low risk	Unclear risk	Unclear risk
	2)	Sample size bigger than calculated by power analysis. (20/24)	Sample size included 30% dropout rate. (46/64)	No sample size calculation performed	No sample size calculation performed
Follow-up time	1)	Low risk	Low risk	Low risk	Low risk
	2)	6 months	12 months	6 months	10 years
Radiographic outcome	1)	Low risk	Low risk	Low risk	Unclear risk
	2)	N/R	N/R	Calibrated and blinded radiologist performed two measurements at an interval of 2 weeks (corr. 93%)	Evaluation process not reported
Clinician bias	1)	Low risk	Low risk	Unclear risk	Low risk
	2)	Trained and blinded examiner different from the surgeons.	One examiner not involved in baseline/surgeries/follow-ups enrolled the participants. Different trained non-blinded examiner (not involved in the surgeries) performed baseline and all follow-up measurements.	All clinical parameters were recorded by one trained periodontist—not mentioned whether this was the surgeon.	All clinical parameters were recorded by an experienced and blinded dental hygienist

(b)		Bianchi and Sanfilippo (2004)	Migliorati et al. (2013) RCT	Yoshino et al. (2014) RCT	Fenner et al. (2016)	Cosyn et al. (2016)	Bienz et al. (2017)
Random sequence generation (selection bias)	1)	High risk	Low risk	Low risk	High risk	High risk	High risk
	2)	Reason for different treatment options not explained. Patients consecutively treated; no randomization.	Randomization generated by statistician (block randomization)	Computer-generated randomization list	According to clinician's judgment (grafting procedure (autogenous) if mucosal thickness was ≤2 mm)	According to clinician's judgment (grafting procedure according to defect as defined by Fürhauser)	Patients were selected for soft tissue grafting procedure for aesthetic reasons by clinician's judgment in a patient pool from an RCT comparing two implant systems
Allocation concealment (selection bias)	1)	NA	Unclear risk	Unclear risk	NA	NA	NA
	2)		Insufficient information	Insufficient information		.	
Blinding of participants and researchers (performance bias)	1)	NA	Low risk	Unclear risk	NA	NA	NA
	2)		The procedure did not allow the surgeon to be blinded for the treatment. (Immediate implant placement with CTG vs no soft tissue graft)	Insufficient information			

(Continues)

TABLE 2 (Continued)

(b)		Bianchi and Sanfilippo (2004)	Migliorati et al. (2013) RCT	Yoshino et al. (2014) RCT	Fenner et al. (2016)	Cosyn et al. (2016)	Bienz et al. (2017)
Blinding of outcome assessments (detection bias)	1)	NA	Low risk	Unclear risk	NA	NA	NA
	2)		Blinded examiners at follow-up time points.	Single examiner			
Incomplete outcome data (attrition bias)	1)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	2)	All expected data are reported. Reason for missing data (four dropouts in 116 patients) undisclosed, but unlikely to be related to outcome.	Loss to follow-up was disclosed (one patient did not comply with the follow-ups).	All expected data are reported. No dropout.	Losses to follow-up were disclosed (1 patient died; six moved or had severe illness).	Losses to follow-up were disclosed (one died; three unwilling to return for follow-up).	No losses. All expected data are reported.
Selective reporting (reporting bias)	1)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	2)	All prespecified outcomes were reported.	All prespecified outcomes were reported.	All prespecified outcomes were reported.	All prespecified outcomes were reported.	All prespecified outcomes were reported.	All prespecified outcomes were reported.
Group imbalance	1)	High risk	Unclear risk	Unclear risk	High risk	High risk	Low risk
	2)	Twenty of 116 implants in control group (no graft) Three test groups according to follow-up time. No further explanation.	Implants of the same type were used and immediately placed with simultaneous GBR-procedure. Twenty-four of 48 patients received an additional autogenous soft tissue graft. According to tissue biotype balanced, location/site not mentioned.	Implants of the same type were used and immediately placed. Allocation/site per group were not mentioned. Thirteen of 20 implants were central incisors.	Even distribution of patients between the groups.	Insufficient information provided.	No group imbalance
Sample size	1)	High risk	High risk	High risk	High risk	High risk	High risk
	2)	No sample size calculation was performed.	No sample size calculation was performed.	No sample size calculation was performed. -> CCT of a previous study	No sample size calculation was performed.	No sample size calculation was performed. Limited sample size.	No sample size calculation was performed. Limited sample size.
Follow-up time	1)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	2)	1–9 years	2 years	1 year	7 years	5 years	5 years

(Continues)

TABLE 2 (Continued)

(b)		Bianchi and Sanfilippo (2004)	Migliorati et al. (2013) RCT	Yoshino et al. (2014) RCT	Fenner et al. (2016)	Cosyn et al. (2016)	Bienz et al. (2017)
Radiographic outcome	1)	High risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
	2)	Evaluation process not reported	Experienced, blinded examiner not involved in the surgeries. Individualized bite blocks.	One examiner performed two measurements at an interval of 3 months. Individualized bite blocks.	Two examiners who discussed until agreement.	Not reported	Not reported
Clinician bias	1)	High risk	High risk	High risk	Low risk	Unclear risk	Low risk
	2)	The study did not address which clinician/s performed the treatments/how patients were categorized/ examiner-blinded	The study did not address which clinicians performed the treatments.	The study did not address which clinician/s performed the treatments/Single examiner	Examiner different from surgeon/that is, previous publication (Jung et al., 2008)	Team of one periodontist and one prosthodontist performed the treatments. Examiner not reported.	Two blinded examiners.

1) Authors' judgment; 2) Support for judgment.

3.4.1 | Keratinized tissue

The four studies (two RCTs, two CCTs) for gain of keratinized tissue reported on a cohort of 234 patients with a mean age of 56.8 (SD 6.7) years. Fifty-eight percent of the patients were females. No patients dropped out in three studies, whereas one study had a dropout rate of 20% (Roccuzzo et al., 2016). All patients were systemically and periodontally healthy at the beginning of the investigations except in one study (Basegmez et al., 2012). In that particular study, patients were included if they presented signs of mucositis. Two studies only included non-smokers, one study light smokers (<10 cigarettes per day; Lorenzo et al., 2012), and one study did not report on smoking habits (Roccuzzo et al., 2016). The overall number of implants included in the studies amounted to 276, and no implant loss was reported (100% implant survival rate) in any of the groups and studies. The mean follow-up time was 36 months (range 6–120 months).

Interventions

The timing of the surgical interventions varied between the studies in terms of the time span following implant placement. The procedures, however, were always performed after the insertion of the final reconstructions. The therapeutic interventions were therefore indicated and performed in patients with existing implants and reconstructions. This included more specifically: implants with (i) signs of mucositis and a width of KT ≤1.5 mm (Basegmez et al., 2012), (ii) a width of KT ≤2 mm (Buyukozdemir Askin et al., 2015), (iii) a width of ≤1 mm (Lorenzo et al., 2012), or (iv) no KM (Roccuzzo et al., 2016).

The types of surgical interventions were as follows: (i) an apically positioned flap or vestibuloplasty procedure alone (APF), (ii) an APF plus a free gingival graft (FGG), (iii) an APF plus a collagen matrix (XCM), or (iv) no treatment (maintenance without intervention) with or without residual keratinized tissue.

Effect of grafting procedure on peri-implant health

Bleeding on probing/Gingival index Two studies reported on "bleeding on probing" (BOP; Buyukozdemir Askin et al., 2015; Roccuzzo et al., 2016), whereas three studies reported on "gingival index" (GI; Loe & Silness, 1963). Final BOP values at the study endpoint were reported to range between 23 and 27% without observing a significant difference between the groups with or without soft tissue grafting in a long-term study (Roccuzzo et al., 2016). In a second study, mean baseline values of 85% (with autogenous soft tissue grafting) and 40%–95% (without soft tissue grafting) and mean study endpoint values of 30% (with autogenous soft tissue grafting) and 25%–95% (without soft tissue grafting) were reported. The changes over time were significant, favoring the group with autogenous soft tissue grafting (Buyukozdemir Askin et al., 2015).

Meta-analyses on study endpoint BOP values revealed no statistically significant difference between groups with and without soft tissue grafting [n = 2; WMD = 0.004; 95% CI (−0.117; 0.125; p = .95]. There appeared to be a tendency, however, favoring grafting with autogenous transplants compared to maintenance within the alveolar mucosa alone [n = 1; WMD = 0.060; 95% CI (−0,124; 0,244); p = .523).

TABLE 3 Original data from the included studies. Study characteristics and interventions

Author	Year of publication	Setting	Study design	Interventions	Test group	Control group 1	Control group 2	Timing of implant placement	Type of implant
Lorenzo et al.	2012	University and Specialist (Two-Centre)	RCT	Augmentation of keratinized mucosa	XCM	SCTG		Implants placed previously; keratinized tissue ≤1 mm	NR
Basegmez et al.	2013	University	RCT	Augmentation of keratinized mucosa	FGG	VP		Implants placed previously (>1 year)	Straumann
Buyukozdemir Askin et al.	2015	University	CCT, prospective	Augmentation of keratinized mucosa	FGG (KT <2 mm)	Maintenance with KT <2 mm	Maintenance with KT>2 mm	Implants placed previously (>1 year)	NR
Roccuzzo et al.	2016	Private Practice	CCT, prospective	Augmentation of keratinized mucosa	Implant placement within AM & FGG	Implant placement within AM	Implant placement within KM	Implants placed previously within KM or AM	Straumann
Bianchi and Sanfilippo	2004	NR	CCT, prospective	Augmentation of soft tissue volume	Immediate implant placement with simultaneous SCTG to facilitate wound closure	Immediate implant placement (no SCTG)		Immediate	Straumann
Fenner et al.	2016	University	CCT, prospective	Augmentation of soft tissue volume	Implant placement with staged SCTG if mucosal thickness was <2 mm	Implant placement (no SCTG if mucosal thickness ≥2 mm)		Immediate, Early, Delayed	Straumann
Yoshino et al.	2014	University	RCT	Augmentation of soft tissue volume	Immediate implant with SCTG	Immediate implant placement (no SCTG)		Immediate	Straumann
Migliorati et al.	2013	University	RCT	Augmentation of soft tissue volume	Immediate implant with SCTG	Immediate implant placement (no SCTG)		Immediate	Straumann

(Continues)

TABLE 3 (Continued)

Author	Year of publication	Setting	Study design	Interventions	Test group	Control group 1	Control group 2	Timing of implant placement	Type of implant
Cosyn et al.	2016	University	CCT, prospective	Augmentation of soft tissue volume	Immediate implant placement with simultaneous GBR; SCTG after 3 months if recession >1 mm	Immediate implant placement with simultaneous GBR (no SCTG)		Immediate	Nobel Active
Bienz et al.	2017	Private Practice	CCT, retrospective	Augmentation of soft tissue volume	Staged implant placement with simultaneous GBR; staged SCTG	Staged implant placement with simultaneous GBR; (no SCTG)		Staged	Straumann (SLA) and Branemark (TiUnite)

RCT, randomized controlled clinical trial; CCT, controlled clinical trial; XCM, xenogeneic collagen matrix; SCTG, connective tissue graft; FGG, free gingival graft; APF, apically positioned flap/vestibuloplasty; KT, keratinized tissue; KT, keratinized mucosa; AM, alveolar mucosa; NR, not reported.

Mean GI values ranged from 0.50 to 1.34 (with soft tissue grafting)/0.35–1.43 (no soft tissue grafting) at baseline to 0.28–0.65 (with soft tissue grafting)/0.20–1.32 (no soft tissue grafting) after follow-up periods of 6–12 months (Tables 3–5). Meta-analysis revealed significant differences between investigated groups for change in GI values ($p < .001$). When comparing change of GI values over time between treatment with an autogenous graft versus maintenance (with or without keratinized tissue), there was a significant difference in favor of the soft tissue grafting group [$n = 2$; WMD = 0.863; 95% CI (0.658; 1.067); $p < .001$] (Buyukozdemir Askin et al., 2015).

Based on the same study, soft tissue grafting leads to significantly reduced final GI values compared to a maintenance group without grafting in sites with a width of keratinized tissue <2 mm [$n = 1$; WMD = 0.670; 95% CI (0.436; 0.904); $p < .001$] (Buyukozdemir Askin et al., 2015).

Probing depth

Probing depth (PD) values did not change significantly over time between the different treatment groups and based on meta-analyses. Mean PD values ranged from 1.97 to 3.09 mm (with soft tissue grafting)/from 1.76 to 3.25 mm (no soft tissue grafting) at baseline and from 2.08 to 3.18 mm (with soft tissue grafting)/from 1.60 to 3.62 mm (no soft tissue grafting) after 6–120 months (Tables 3–5). Comparing final PD values for group APF versus APF plus autogenous tissue resulted in significantly lower values favoring group APF plus autogenous tissue [$n = 1$; WMD = 0.440; 95% CI (0.223; 0.657); $p < .001$].

Marginal bone level changes

Marginal bone level and the respective changes were reported in one of four studies (Buyukozdemir Askin et al., 2015), whereas one study reported on final values only (Roccuzzo et al., 2016). In the first study, no significant differences were observed over time between sites with or without soft tissue grafting based on meta-the analysis on marginal bone loss [$n = 1$; WMD = −0.025; 95% CI (−0.108; 0.058); $p = .553$]. Mean marginal bone level changes were 0.16 mm (with soft tissue grafting) and 0.21 mm (for maintenance with <2 mm KT) and 0.15 mm (for maintenance with >2 mm KT) during an observation period of 6 months (Tables 3–5).

Statistically significant differences were noted for final marginal bone levels in favor of APF plus autogenous grafts versus all control treatments (apically positioned flap or vestibuloplasty procedure alone (APF); APF plus a collagen matrix (XCM); no treatment (maintenance without intervention) with or without residual keratinized tissue) [$n = 4$; WMD = −0.175; 95% CI: (−0.313; −0.037); $p = .013$]. These differences were predominantly based on the differences between APF plus autogenous grafts versus maintenance within keratinized tissue [$n = 3$; WMD = −0.213; 95% CI (−0.373; −0.054); $p = .009$)].

Plaque index

Three studies reported plaque index values at baseline and at follow-up time-points of 6–12 months (Basegmez et al., 2012; Buyukozdemir Askin et al., 2015; Roccuzzo et al., 2016; Tables 3–5). In two studies,

TABLE 4 Original data from the included studies. Patient characteristics and sample size

Author	Year of publication	Gender (% female)	Inclusion criteria	Smoking	Systemic condition	Sample size (Baseline/ Final)	Test patients (Baseline/ Final)	Control patients (Baseline/Final)	Follow-up (months) (range)	Dropout (%)	Mean age (months)
Lorenzo et al.	2012	NR	Full-mouth Plaque score <20%	<10 Cig/day	Systemically healthy	24	12/12	12/12	6 (NR)	0	63
Basegmez et al.	2013	56%	Peri-implant mucositis	0	Systemically healthy	64/64	32/32	32/32	12 (NR)	0	59.92 (SD 10.96)
Buyukozdemir et al.	2015	55%	Periodontally healthy (Full-mouth PII & GI <15%)	0	Systemically healthy; no medication	18 patients/60 implants	20/20 (Impl)	20/20 (Impl) **C1** 20/20 (Impl) **C2**	6 (NR)	0	74.5 (SD 11.26)
Roccuzzo et al.	2016	62%	NR	NR	NR	129/98	0/11	42/24 **C1** 86/63 **C1**	120 (NR)	20%	NR
Bianchi and Sanfilippo	2004	50%	NR	NR (<15Cig/d)	No alcohol or drug abuse	116/116	96/96	20/20	NR (12–108)	0	45.4 (19–73)
Fenner et al.	2016	45%	Periodontally healthy	6	Two mental disorder, one osteoporosis, one tumor, two high blood pressure, one neurodermitis	36/28	14/13	22/15	86.4 (63.6–111.6)	22.3%	48 (27–82)
Yoshino et al.	2014	65%	Periodontally healthy	0	Systemically healthy	20/20	10/10	10/10	12 (NR)	0	52.6 (22–87)
Migliorati et al.	2013	52%	Periodontally healthy	2 (<5 Cig/d)	Systemically healthy	48/47	24/24	24/23	24 (NR)	2%	47.5 (22–70)
Cosyn et al.	2016	45%	Periodontally healthy	None (Exclusion criteria)	NR	22/17	7/5	15/12	60 (NR)	6%	50 (27–74)
Bienz et al.	2017	61%	Periodontally healthy	2	Systemically healthy	18	8/8	10/10	60.6 (53–152)	0	59.4 (27–76.6)

Control Group 1 = C1
Control Group 2 = C2
Mean age in months with range or standard deviation (SD); PII, plaque index; GI, gingival index; smokers: number of patients; NR, not reported.

TABLE 5 Original data from the included studies. Clinical parameters (BOP, GI, PPD, mBL, PII)

				BOP/GI		PPD		mBL		PII	
Author	Year of publication	Sample size (Test/Control)	Follow up (Months)	Baseline (Test/Control)	Final (Test/Control)	Baseline (Test/Control)	Final (Test/Control)	Baseline (Test/Control)	Final (Test/Control)	Baseline (Test/Control)	Final (Test/Control)
Lorenzo et al.	2012	24 (12/12)	6 (NR)	0.50/0.73	0.33/0.20	2.08/2.00	2.08/1.60	NR	NR	NR	NR
Basegmez et al.	2013	64 (32/32)	12 (NR)	1.34/1.43	0.28/0.37	3.09/3.25	3.18/3.62	NR	NR	1.56/1.25	0.18/0.28
Buyukozdemir et al.	2015	60 (20/20/20)	6 (NR)	85%/ 85% **C1** 40% **C2** 1.33/ 1.17 **C1** 0.35 **C2**	30%/ 95% **C1** 25% **C2** 0.65/ 1.32 **C1** 0.56 **C2**	1.97/ 1.76 **C1** 2.05 **C2**	2.29/ 2.29 **C1** 2.43 **C2**	−0.39/ −0.6 **C1** −0.56 **C2**	−0.55/ −0.81 **C1** −0.72 **C2**	0.58/ 0.38 **C1** 0.16 **C2**	0.21/ 0.45 **C1** 0.06 **C2**
Roccuzzo et al.	2016	98 (11/24/63)	120 (NR)	NR	27%/ 33% **C1** 23% **C2**	NR	2.95/ 2.77 **C1** 3.13 **C2**	NR	0.56/ 0.50 **C1** 0.34 **C2**	NR	0.27/ 0.38 **C1** 0.21 **C2**
Bianchi and Sanfilippo	2004	116 (96/20)	NR (12–108)	NR	69%=0 26%=1 4%=2 / 70%=0 20%=1 9%=2	2.5/2.5	27% of implants > 3 mm / 45% of implants > 3 mm	NR	80% < 3.5 mm/34% < 3.5 mm	NR	57%=0 29%=1 9%=2 / 57%=0 29%=1 9%=2
Fenner et al.	2016	28 (13/15)	86.4 (63.6–111.6)	NR	56%/46%	NR	4.09/3.97	NR	2.50/2.20	NR	0.15/0.28
Yoshino et al.	2014	20 (10/10)	12 (NR)	NR	0 = 7 impl **T** 1 = 3 impl **T** 0 = 10 impl **C**	NR	NR	−0.06/−0.17	−0.07/−0.31	NR	0 = 8 impl 1 = 2 impl (for **T** & **C**)
Migliorati et al.	2013	47 (24/23)	24 (NR)	20%/40%	20%/40%	3.30/3.20	3.40/3.20	Change −0.06/−0.16		0.1/0.2	0.1/0.1
Cosyn et al.	2016	17 (5/12)	60 (NR)	29%/21%	30%/33%	NR	NR	NR	NR	NR	NR
Bienz et al.	2017	18 (8/10)	60.6 (53–152)	35%/35%	38%/38%	3.45/2.76	3.67/3.65	NR	NR	0.08/0.14	0.10/0.14

BOP, bleeding on probing; GI, gingiva index; PPD, probing pocket depth; mBL, mean marginal bone level; PII, plaque index; NR, not reported. Mean values are given at Baseline (Baseline) and at the respective final follow-up (Final).

for Buyukozdemir et al.: C1, maintenance with <2 mm KT; C2, maintenance >2 mm KT).

for Roccuzzo et al.: C1, no treatment (maintenance without intervention) *without* residual keratinized tissue (implants were placed within alveolar mucosa); C2, no treatment (maintenance without intervention) *with* residual keratinized tissue (implants were placed within keratinized tissue).

a significant benefit with lower plaque values was observed following the surgical intervention to increase KT (Buyukozdemir Askin et al., 2015; Roccuzzo et al., 2016), whereas one study reported a significant decrease of the plaque index over time, but no significant difference compared to the untreated control group at baseline and at 12 months (Basegmez et al., 2013). Meta-analysis for these data indicated significant differences in final PII values when comparing APF plus autogenous grafts versus with maintenance (KT<2 mm), favoring the grafted group [n = 1; WMD = 0.240; 95% CI (0.002; 0.478); p = .049]. Performing a grafting procedure reduced PII value changes comparing maintenance groups (KT<2 mm or >2 mm) and APF versus APF plus autogenous grafts [n = 3; WMD = 0.354; 95% CI (0.228; 0.480); p < .001).

Superiority of one grafting procedure/material over others/gain in width of keratinized tissue (KT)

Three treatment modalities (autogenous tissue, collagen matrix, and apically positioned flap [AFP]) were used in the four included studies and compared with regular maintenance of implant sites with more than 2 mm, less than 2 mm, or no keratinized tissue. Statistically significant differences favoring APF plus autogenous tissue were observed for final PPD values (vs. APF) only (p < .001). All other parameters did not reveal to favor any treatment in terms of peri-implant health. These data were derived from one clinical study and a reported observation period of 6 months.

3.4.2 | Mucosal thickness

The six studies (two RCTs, four CCTs) reporting on surgical interventions for gain of mucosal thickness included 260 patients with a mean age of 50.5 (±4.6) years (Table 1). Fifty-three percent of the patients were females. The mean dropout rate was 5% (0% in three studies). All patients were systemically and periodontally healthy. One study, however, did not report on the general and periodontal health of the patients (Bianchi & Sanfilippo, 2004). Included patients were smokers of <15 cigarettes per day (Bianchi & Sanfilippo, 2004), <6 cigarettes per day (Bienz et al., 2017; Fenner et al., 2016; Migliorati et al., 2015), or were non-smokers (Cosyn et al., 2016; Yoshino et al., 2014). The overall number of implants assessed amounted to 260 at baseline and 246 at the follow-up examinations. No implants were reported to be lost (100% implant survival rate) in any of the groups and studies. The mean follow-up time was 40.5 months (range 12–86 months).

Interventions

In five studies, immediate implants were placed, whereas in one study, delayed implant placement was performed (Bienz et al., 2017). The mucosal thickness was increased at implant placement (Bianchi & Sanfilippo, 2004; Migliorati et al., 2015; Yoshino et al., 2014) or >3 months postimplant placement (Bienz et al., 2017; Cosyn et al., 2016; Fenner et al., 2016). All procedures were therefore performed prior to the insertion of the final reconstructions. The therapeutic interventions were reported to be indicated as follows: (i) to prevent recessions and compensate for volume deficiency (Cosyn et al., 2016), (ii) to facilitate tissue adaptation at implant placement (Bianchi & Sanfilippo, 2004), (iii) for aesthetic purposes and to compensate for volume deficiencies (Bienz et al., 2017; Fenner et al., 2016), or (iv) not further mentioned (Migliorati et al., 2015; Yoshino et al., 2014).

The type of surgical interventions was as follows: (i) immediate implant placement without soft tissue grafting, (ii) delayed implant placement without soft tissue grafting, (iii) immediate implant placement plus simultaneous subepithelial connective tissue graft (SCTG), (iv) immediate implant placement plus delayed SCTG, or (v) delayed implant placement plus delayed SCTG.

Effect of grafting procedure on peri-implant health

Bleeding on probing Four studies (Bienz et al., 2017; Cosyn et al., 2016; Fenner et al., 2016; Migliorati et al., 2015) reported on BOP values. Mean values ranged between 20 and 35% (autogenous soft tissue grafting); 21%–40% (no grafting) at baseline and 20%–56% (autogenous soft tissue grafting); 33%–46% (no grafting) after a mean follow-up of 57 months (Tables 3–5). Meta-analysis did not demonstrate any significant influence of grafting procedures on BOP values compared to control groups, neither for changes over time nor for endpoint values.

Probing depth

In five studies, no significant effect after soft tissue volume augmentation was observed, with mean PD values ranging from 2.50 to 3.45 mm (with grafting); from 2.50 to 3.20 mm (without grafting) at baseline to 3.67–4.09 mm (with grafting); 3.20–3.97 mm (without grafting) after a mean of 57 months (Tables 3–5). One study reported a significant benefit (lower PD values) following an increase in mucosal thickness (Bianchi & Sanfilippo, 2004). In that particular study, 27% of the test implant sites (immediate implants with soft tissue grafting) as compared to 45% of the control implant sites (without soft tissue grafting) had PD values >3 mm (Bianchi & Sanfilippo, 2004). Meta-analysis did not reveal any significant differences regarding PD between grafted (autogenous graft) and control groups (no grafting).

Marginal bone level changes

Marginal bone level changes and final values were reported in two of four studies (Migliorati et al., 2015; Yoshino et al., 2014). Final values were reported in two studies (Fenner et al., 2016; Yoshino et al., 2014; Tables 3–5). Groups without soft tissue grafting lost significantly more marginal bone over time than groups with grafting (WMD = 0.110; 95% CI: 0.067; 0.154; p < .001). Meta-analysis demonstrated a borderline significance favoring soft tissue grafting [n = 2; WMD = 0.249; 95% CI (−0.001; 0.500); p = .051] for final marginal bone levels.

Plaque index

Plaque values were assessed in all six of the included studies. None of the studies reported any significant differences between implants sites that had undergone a soft tissue grafting procedure and the respective control (non-grafted) sites. Moreover, plaque index values

remained stable independent of any surgical intervention, the timing of soft tissue grafting (at implant placement or staged), and study design (CCT or RCT) with reported mean follow-up periods between 12 and 108 months (Tables 3–5). Similar results were obtained applying meta-analysis, finding no statistically significant differences for change of PII values between grafted and non-grafted groups [n = 1; WMD = 0.020; 95% CI (−0.174; 0.214); p = .840].

Superiority of one grafting procedure/material over others

In all six included studies, subepithelial connective tissue grafts were used to increase the mucosal thickness. No other materials such as soft tissue substitutes were applied. No superiority of any treatment modality could therefore be calculated. The time-point of implant placement as well as the time-point of soft tissue grafting differed between the studies. Due to heterogeneity in terms of study design (CCT, RCT) and reported outcome measures, an ideal time-point for implant placement in conjunction with soft tissue augmentation (immediate, early, delayed) or soft tissue grafting (simultaneous with implant placement or staged) could not be assessed.

4 | DISCUSSION

The present systematic review assessed the influence of soft tissue grafting procedures on peri-implant health. The outcomes revealed that soft tissue grafting using autogenous tissue for gain of keratinized tissue results in (i) a significant decrease of BOP and GI values and significantly lower GI values at the study endpoint compared to maintenance groups; (ii) significantly lower PD values compared to APF alone; (iii) significantly higher marginal bone levels at the study endpoint compared to control groups; and (iv) a significant decrease of PII values and significantly lower PII values at the study endpoint compared to control groups.Soft tissue grafting using SCTGs to augment the mucosal thickness resulted in (i) no significant improvement over time nor at the study endpoint for BOP, PD, and PII values; (ii) significantly less marginal bone loss over time and a borderline significance for marginal bone levels at the study endpoints compared to sites without grafting.

4.1 | Keratinized tissue

Various procedures and materials were evaluated in the past to augment keratinized tissue around teeth and dental implants predominantly with the purpose to obtain health of periodontal and peri-implant tissues (Thoma, Benic, Zwahlen, Hammerle & Jung, 2009; Thoma et al., 2014). BOP and GI values are considered valuable measurements to assess peri-implant health (Heitz-Mayfield, 2008; Salvi & Lang, 2004; Zitzmann & Berglundh, 2008). These values also serve as indicators for changes of the biological peri-implant environment and the development of peri-implant mucositis, a reversible disease of the peri-implant tissues (Jepsen et al., 2015; Salvi et al., 2012). In case of increased or increasing BOP and GI values, various surgical techniques were proposed to increase the width of keratinized tissue, thereby establishing peri-implant health and thus preventing the development of peri-implant disease. Data based on the present meta-analyses revealed a significant improvement in the primary outcome BOP/GI over time and significantly lower GI values at the follow-up time-points following grafting with autogenous tissue. Moreover, PD and PII values decreased, and marginal bone levels were higher for groups with surgical interventions. These results demonstrate that soft tissue grafting procedure results in biologic benefits compared to control groups and thereby justify the surgical interventions. This is in line with previous publications using a retro- or prospective design (Bouri et al., 2008; Schrott et al., 2009). Data from more recent systematic reviews on the topic of keratinized tissue gain around dental implants were more controversial and not able to fully support these surgical interventions to maintain or enhance peri-implant health (Chiu, Lee, Lin & Lai, 2015; Gobbato, Avila-Ortiz, Sohrabi, Wang & Karimbux, 2013; Wennstrom & Derks, 2012). The observed clinical benefit (based on the present systematic review) in favor of soft tissue grafting procedure might in part be explained by the fact that the presence of keratinized tissue results in a more stable seal around the implant neck that facilitates the ability of the patients to clean the reconstructions and to limit bacterial infiltration. This is in line with a recent clinical study demonstrating that implant sites with less than 2 mm of keratinized tissue were more prone to brushing discomfort, plaque accumulation, and peri-implant soft tissue inflammation compared to implant sites with ≥2 mm of keratinized tissue (Souza, Tormena, Matarazzo & Araujo, 2016).

Even though for various transplants and soft tissue substitutes (autogenous tissue, collagen matrix, and apically positioned flap [AFP]) were evaluated in the included studies, comparative analyses of different procedures revealed significantly more favorable data for APF plus autogenous tissue versus APF alone only. All other assessed parameters did not show any benefit of one treatment modality over another. Hence, clinical recommendations can only be made for APF plus autogenous tissue and not for any other treatment modality at the current moment.

The obtained data need to some extent be interpreted with caution based on a number of facts: (i) heterogeneity between the studies in terms of groups, assessed outcome measures, follow-up time-points and, (ii) the inclusion of CCT trials and the respective high risk of bias for the majority of the questions related to the quality assessment. Heterogeneity between the studies not only encompassed the study design (RCT vs. CCT), but further included the number of patients, sites, the assessed outcome measures (BOP, GI), the time-point of the clinical examination and the follow-up period. These limitations resulted in few outcomes that were eligible for meta-analyses based on few included studies and heterogeneous study designs.

Moreover, the literature is scarce in terms of controlled clinical studies comparing surgical procedures for gain of keratinized tissue including the, from a biologic point of view, most important outcome of inflammation (BOP/GI) at peri-implant sites. This is rather surprising and was the predominant reason for exclusion (in 17 of 23) of full-text articles. Efforts should therefore be undertaken to include such outcome measures in future randomized controlled clinical trials.

4.2 | Mucosal thickness

Soft tissue grafting procedures intended to increase the mucosal thickness were predominantly performed to improve the aesthetic outcome and to compensate for existing volume deficiencies (Bienz et al., 2017; Cosyn et al., 2013; Fenner et al., 2016). Only recently, similar procedures were proposed to target a biologic effect, for example, minimizing marginal bone loss around dental implants (Linkevicius, Puisys, Linkeviciene, Peciuliene & Schlee, 2015). In all included clinical studies of the present systematic review, autogenous connective tissue grafts were used and control groups included non-grafted implant sites. The primary outcome of the present systematic review, assessing BOP/GI values, could not demonstrate any significant influence of soft tissue grafting procedure on peri-implant health or disease. Consequently, such surgical interventions might, at the moment and based on very scarce clinical data, not be recommended to positively influence the peri-implant tissues on the biologic level. Interestingly, marginal bone level changes (significant) and endpoint levels (borderline significant), however, demonstrated more favorable results for groups with soft tissue grafting compared to untreated controls. This is in line with short-term results from a clinical study where the presence of a thick (both originally existing and after augmentation with an allograft) peri-implant mucosa led to higher marginal bone levels compared to implant sites with a thin mucosa (Linkevicius et al., 2015). Meta-analyses were based on three eligible studies reporting on changes (two studies) and final marginal bone levels (two studies). These results underline, to some extent, that the data need to be interpreted with caution due to heterogeneity in study design (RCT vs. CCT) and a limited number of included studies. Moreover, the reported borderline significance for final marginal bone levels favoring soft tissue grafting is based on one long-term (7.2-years) study indicating a benefit (Fenner et al., 2016), and a second study reporting a negative effect (Yoshino et al., 2014) of SCTGs on peri-implant marginal bone levels at a 1-year follow-up. These results were not statistically significant in the original publications, whereas they were borderline significant based on the meta-analysis and must be interpreted with caution due to varying follow-up periods.

4.3 | Limitations of the systematic review

The present systematic review covered a new area of research area, and the number of publications found through online, and hand search was therefore limited. The database "MEDLINE" was selected for the electronic search, and thus, the search was based on one database only, although knowing that more databases exist. One might thus speculate that more scientific data exist and might therefore consider this a limitation of the present systematic review. This possible lack was, however, compensated by an additional hand search that included the thorough screening of narrative and systematic review articles, and the, reference lists of all obtained full-text articles even the ones that were later excluded. No further hand search of journals was performed though.

Additionally, the unit of analysis was pooled for the meta-analysis for the sake of the small number of included studies. Although most of the included studies had analyzed their data on the patient level, two studies had used the implant as the unit of analysis. From a methodological point of view, this is an important limitation, as implant-level analysis tends to underestimate the confidence intervals for the pooled estimate, yielding to an inflated type-I error.

The initial search (limited to one database only and the absence of a grey literature search) provided a relatively high number of potentially eligible studies. Most of these studies, however, did not provide data on bleeding indices, even after contacting the corresponding authors, as their primary focus was aesthetics or changes of marginal bone levels (Cornelini et al., 2008; Grunder, 2011; Linkevicius et al., 2015). Given these to some extent limited data, clinical recommendations include that in general, the clinician may consider the use of autogenous soft tissue grafting to promote peri-implant soft tissue health or marginal bone levels at implant sites with insufficient soft tissue dimensions. It is anticipated that plaque control is better facilitated in the presence of >2 mm of keratinized tissue. In case an increase of keratinized tissue is desired around a dental implant, the clinician should consider performing a free gingival graft. In the esthetic zone, when an increase in mucosal thickness around implant sites displaying volume deficiencies is desired, clinicians should consider connective tissue grafting procedures to promote greater stability of interproximal marginal bone levels.

5 | CONCLUSIONS

Soft tissue grafting procedures can be recommended to improve peri-implant health. For gain of keratinized tissue, the use of an apically positioned flap in conjunction with autogenous grafts resulted in a greater improvement of bleeding indices and higher marginal bone levels. For gain of mucosal thickness, the use of autogenous grafts resulted in significantly less marginal bone loss over time, but no improvement of further clinical parameters (e.g., bleeding indices).

CONFLICT OF INTEREST

The authors report no conflict of interest with respect to the publication of this article.

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